

Rheoencephalography (REG) as a Non-Invasive Monitoring Alternative for the Assessment of Brain Blood Flow

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ABSTRACT

This work focuses on exploration of the potential use of pulsatile brain bioimpedance (rheoencephalography - REG) measurement as a non-invasive, continuous method for assessing the status of cerebral blood flow (CBF) in combat casualties.

1.0. INTRODUCTION

1.1. Relevance

An important goal of the Army's Medical Department is to develop physiological monitoring of parameters that will aid in the assessment and treatment decisions of combat casualties. The two most frequent causes of death in combat are exsanguination (44 %) and central nervous system injury (31 %) [1]. Development of devices for early noninvasive monitoring of multiple parameters in the field is required for expedient and effective triage and treatment decisions [2]. The superiority of a resuscitation strategy that targets maintenance of CBF and function in the context of cardio-pulmonary resuscitation has been demonstrated by P. Safar and used in the emergency medical practice [3].

1.2. Rationale - Pathophysiology

Systemic hypotension, brain ischemia and hypoxia can cause brain damage mediated by microvascular changes. Monitoring CBF or cerebrovascular reactivity is applied in neurosurgical clinical practice in order to

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evaluate the status of the patient after brain injury or operation. The concept of CBF thresholds of ischemia was introduced in the seventies when it was observed that a more dense zone of ischemia exists within the central core of the ischemic zone, but in the peripheral zones, where electrical silence may pertain, there is a zone of intact ionic homeostasis, which has been termed the “ischemic penumbra”. The flow threshold for maintenance of electrical activity in the cortex is 15-20 ml/100g/min [4,5] and an ultimate goal for resuscitation from hemorrhagic hypotension is to maintain the CBF above this level.

1.3. Broader View

The application of REG for potential military applications began at the Walter Reed Army Institute of Research over 40 years ago [6,7]. Authors found characteristic changes in the REG wave with increased intracranial pressure in humans and in animals, furthermore complained about the manual control of REG amplifier. Since that time advances in the development of microprocessors and signal processing techniques has presented the possibility to reconsider the feasibility of implementing a portable or even wearable version of the rheoencephalography monitoring technique to evaluate the adequacy of brain blood flow [8]. Our goal is to develop a non-invasive approach to monitoring brain blood flow that would serve as an important component of assessing the severity of injury and as an end-point for resuscitation. Use of REG as a wearable monitoring system would allow life-saving assessment and treatment during the first critical minutes after injury during the transport of a wounded soldier.

1.4. This Study

In the animal studies reported here, we monitored and compared global CBF using REG, local CBF by laser Doppler flow, and carotid flow by Doppler ultrasound during physiological stimuli known to produce predictable changes in CBF.

2.0. METHODS

Research was conducted in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NRC Publication, 1996 edition.

2.1. Rats (Group 1)

In this group two studies were undertaken in anesthetized rats to study the changes CBF using two standard perturbations: 1) CO₂ and O₂ inhalation and 2) electrical stimulation of the brain.

Brain electrical impedance was recorded in 8 male Wistar rats anesthetized with pentobarbital and ventilated with 30% O₂ (balance N₂). Stainless steel needle electrodes were implanted into the brain and fixed with dental cement. These REG recordings were made by monitoring impedance shifts with bipolar (intrahemispherical) or tetrapolar (interhemispherical) techniques with an excitation frequency of 50 kHz (Model 2991 and 2994, UFI, Inc. Morro Bay, CA). CBF levels were altered by changing the inspired gas mixture for one minute (one mixture for one minute; 100% O₂, 5% CO₂, and 20% CO₂) or by applying electrical pulses (20 Hz, 0.5 msec pulse duration, 2 sec pulse trains with intensity varied to produce an effect, i.e. max 15 sec, ramped up by 10 V for each trial until CBF increased, max 60 V, and 3 trials) directly to the exposed cerebral surface of one hemisphere. The stimulating electrodes were covered with dental cement, also. REG measurements and DC impedance (R_o) were recorded simultaneously on a portable IBM compatible computer using CODAS (DATAQ, Inc., Akron, OH) data acquisition system. Data collection for

analysis lasted 4 min, covering a baseline, gas administration or electrical stimulation and recovery. Each of the recorded signals was digitized at a rate of 250 Hz using a 12-bit A/D conversion board. The signals were processed by Rheosys software. Data were quantified using the recorded pulsatile and basal resistance values, as described earlier [9].

2.2. Rats (Group 2)

In this study in anesthetized rats, various CO₂ concentrations were used to study CBF reactivity.

REG signals were recorded in female Wistar rats anesthetized with pentobarbital (N = 5, 13 measurements; some rats were used more than once). Stainless steel needle electrodes were implanted into the brain and fixed with dental cement. These measurements were made prior to, during and after 2-min substitutions of varying fractions of CO₂ (4%, 6%, 8% or 10%) for N₂ in the inspired gas mixture. The REG measurements were made using a rheograph (ReoRon-61; Mikromed, Esztergom, Hungary). The measuring frequency was: 160 kHz, sensitivity: 0.03 ohm. The REG and electrocardiogram signals were connected to the analog memory recorder (MCAM-4, Rolitron, Budapest, Hungary). The data processing of the above-mentioned modalities was signal averaging (n = 40 pulses in about 10 sec), triggered by the R-peak of the EKG. The basis of comparison was the change of amplitude, integral and ascending portion of the REG curve during different concentrations of CO₂ inhalation compared to baseline.

2.3. Rat (Group 3)

In this group three correlative studies were undertaken on anesthetized rats to study CBF responses to the following perturbations: 1) CO₂ inhalation, 2) carotid clamping, and 3) hemorrhage to 40 mmHg.

Sprague-Dawley rats (250-350 g) were anesthetized with sodium pentobarbital IP (50 mg/kg), heparinized (50 IU/100g, IV), a tracheostomy performed and body temperature maintained with a closed loop heating pad-rectal thermometer system (Homeostatic Blanket Control Unit, Harvard Apparatus, Edenbridge, KT). One femoral artery was used for heart rate and blood pressure, and the other was attached to a peristaltic pump for hemorrhaging the animal. The controlled hemorrhage model was a modified Wiggers isobaric shock model in which the animal's mean arterial blood pressure is reduced at a precise rate, under computer control, to a target mean arterial pressure of 40 mmHg, and then held there until experimental intervention, resuscitation, decompensation or death occurred. The experiment was performed using a computer-based data acquisition system, running a program written in LabView (National Instruments, Houston, TX). REG was measured with intracranial electrodes (Plastics One, Roanoke, VA) with 5 mm uninsulated surface in intrahemispheric derivation (left or right side) (see Fig. 1). The composition of the CO₂ inhaled gas used for the challenge was 10 % CO₂ (Calibrating Gas, Nova Biomedical, Waltham, MA; 10% CO₂, 0% oxygen, 90% N₂) for 1 s. The total number of rats measured by REG during CO₂ inhalation was n=11, in 63 trials. Here we present results of two subgroups (A: n = 4, trials = 32, B: n=5, 17 trials). Occlusion of the common carotid arteries was accomplished using aneurysm clips or carotid ligatures, while the rat was in the supine position (n=5, 13 trials). Readings from the Doppler flow probes verified the lack of blood flow through the carotid arteries, Fig. 2. During hemorrhage mean blood pressure was 40 mmHg. Measurement of CBF was taken with REG (n=14), laser Doppler flowmetry (Integrating probe, Periflux System 4001, Perimed Sweden), (LDF; n=4), and carotid flow by Doppler ultrasound (T201 Ultrasonic Bloodflow Meter, Transonic Systems, Ithaca, NY), (n=11).

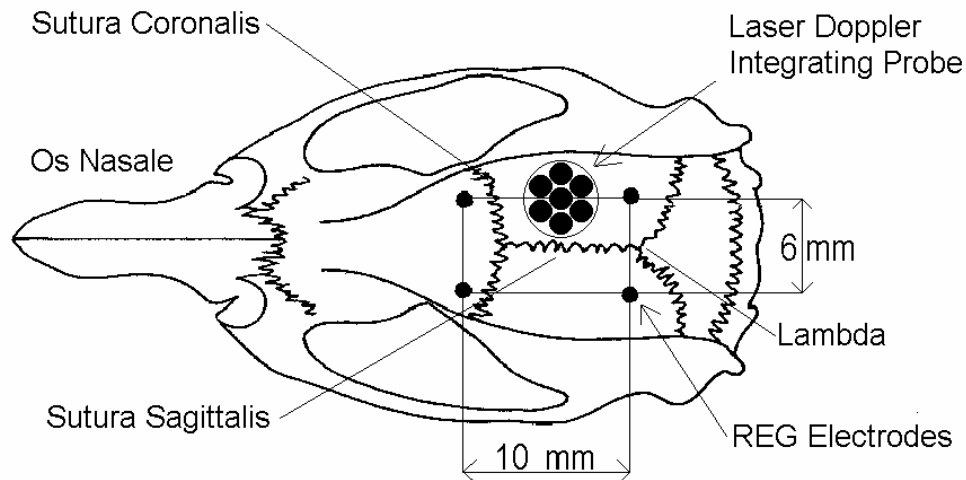


Figure 1. Rat skull with electrode and probe localization.

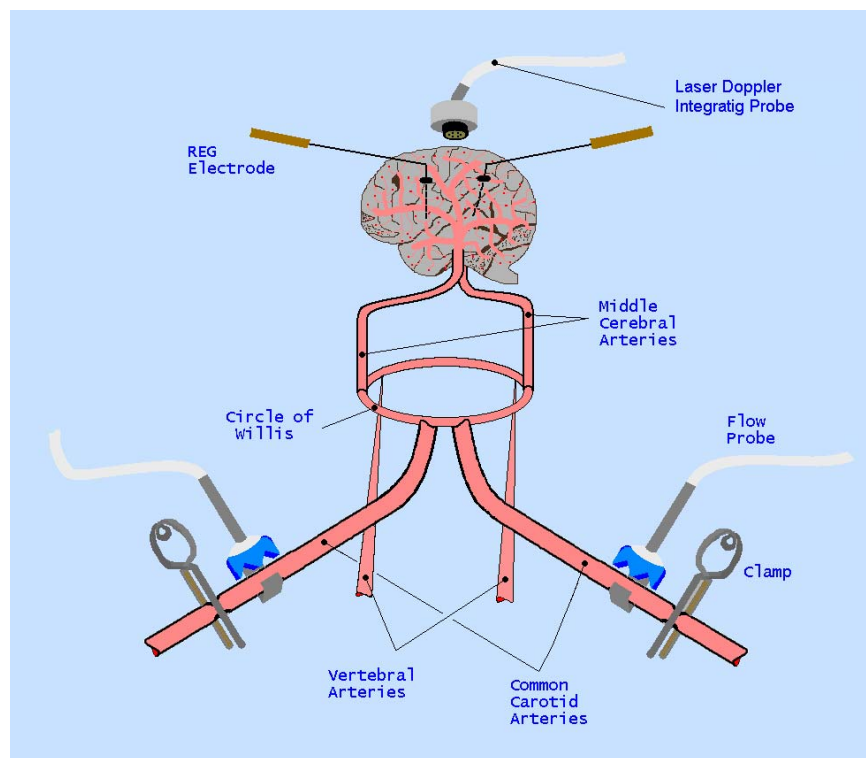


Figure 2. Schematics of CBF, global (REG), local (LDF) and carotid flow measurement.

2.4. Pig

A 22 kg pig was anesthetized with ketamine and acepromazine (iv). The pig was instrumented with a LDF probe over the parietal cortex (19 mm AP, 10 mm Lat.). The probe was inserted through a hollow cranial bolt, and contacted bone was thinned to translucency. The local CBF was measured by a LDF monitor

(VasaMedics, St. Paul, MN) with 3 second averaging. Arterial blood pressure (BP) was also measured via catheterization of the femoral artery. BP was measured using a pressure transducer connected to a pressure amplifier ((23XL, Gould Instrument Systems, Valley View, OH). Baseline mean BP was 62 mmHg; this value was considered as 100 percent. The REG was measured by placing 9 mm diameter stainless steel disc electrodes on the skull over the parietal cortex. The probes were held in place by 0-80 x 3/16" stainless steel screws. A conductive gel was used to decrease resistance between the electrode and the skull. To investigate autoregulation of CBF with varying SAP a series of temporary (5 min) aortic occlusions (n = 4) were performed proximal to the kidneys. SAP, LD and REG were continuously collected before, during, and after each occlusion.

2.5. Challenges

CBF was altered with the following manipulations: CO₂ inhalation [10,11], brain electrical stimulation [12], ligation of the common carotid arteries [13,14], and hemorrhage in rats, furthermore aorta compression [15] in swine.

2.6. Data Acquisition

Unless noted otherwise, the REG amplifier was operated with 46 kHz (KR-Rheo Preamp, Galileo, Italy). An IBM compatible PC performed the data collection with a PC-LPM-16 (National Instruments, Austin, TX), or PCL-718 AD card (Advantech, CA). The A/D sampling rate was 100-500 Hz. For analog physiological data acquisition, proprietary software (Analyze, Chart, Extract, Gral [16], Redirec [17], DataLyser) was used on a PC and the data processed off line. The REG, LDF and carotid flow calculation and comparison was analyzed quantitatively, based on amplitude (minimum - maximum distance of a REG pulse) and integral (area under the pulse curve) measurement of 5 to 10-sec time-windows. Since neither LDF nor REG is an absolute flow measurement, a control segment of recording was chosen from the pretreatment period (baseline), and the changes were expressed as a percentage of baseline. In order to decrease the respiratory interference with REG, the data was digitally filtered (Butterworth band pass, 0.3-60 Hz, 512 point, 60 dB; with a software module integrated into the DataLyser software (Baranyi, WRAIR).

2.6.1. Statistical Analysis

Student t-test, Pearson's linear correlation, and Spearman's rank correlation were utilized within the Minitab software for data analysis. Pearson's correlation coefficient indicates the strength of a linear relationship, and Spearman's rank correlation indicates the strength of a monotonic relationship. The P-values indicate how likely it is that the coefficients are equal to zero (i.e. the null hypothesis tested is that each coefficient is equal to zero). $P < 0.05$ was considered significant.

3. 0. RESULTS

3.1. Rat/1

3.1.1. Brain Electrostimulation

Electrical stimulation caused a REG amplitude increase in the ipsilateral (but not the contralateral) hemisphere Fig. 3.

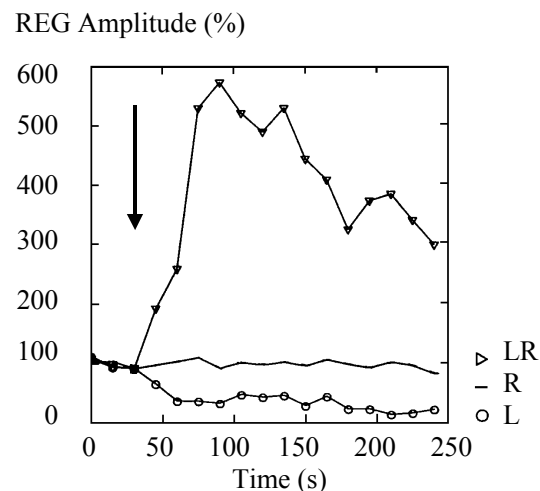


Figure 3. Typical maximal REG amplitude responses to electrical stimulation of the right hemisphere. Stimulation produced a marked increase in REG pulse amplitude of the stimulated hemisphere and a possible decrease in pulse amplitude of the non-stimulated left hemisphere. These responses would not likely be detected by monitoring the total CBF. The time of the stimulation is indicated by downward arrow. Y-axis units are in percentage of baseline. Legend: left (oL), right (-R), and combined left and right (∇ LR); mean of 3 runs on one rat ([18] with permission).

3.1.2. CO₂ Inhalation

When 5% CO₂ was substituted for the equivalent fraction of N₂ in the inspired gas mixture, there were no significant changes in the REG amplitude, indicating that this treatment was without effect on CBF. The substitution of 20% CO₂ for the equivalent fraction of N₂, however, markedly increased the REG signal amplitude, indicating increased CBF, Fig. 4.

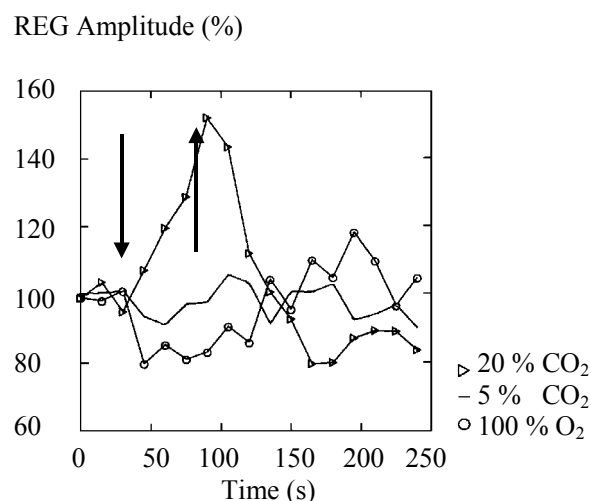


Figure 4. REG amplitude prior to, during, and following 2 min of 100% O₂, 5% CO₂, and 20% CO₂ inhalation. The time of the start and stop of the gas administration is indicated by downward and upward arrows, respectively. Inspiration of 100% oxygen (o) produced a slight decrease in REG amplitude. Inspiration of 5% CO₂ (-) with 30% O₂ did not affect REG amplitude. Breathing 20% CO₂ (Δ) with 30% O₂ produced a 50% increase in REG amplitude. Y-axis units are in percentage of baseline ([18] with permission).

3.2. Rat/2

During CO₂ inhalation a linear relationship was established between CO₂ concentration and REG peak amplitude (correlation coefficient: 0.88, $p = 0.05$), and the raise time (anacrotic portion) of the curve (0.88, $p = 0.05$), Fig. 5.

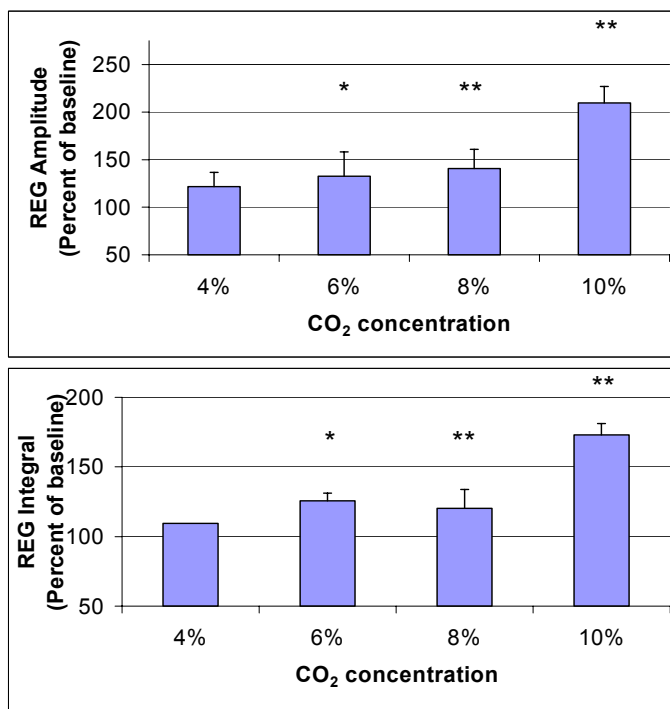


Figure 5. Increase of REG amplitude (upper) and integral (lower) during inhalation of various CO₂ concentrations. Y-axis values are percentage of baseline. Data are mean + SD. Statistical significance (compared to baseline) is expressed as: * = $p < 0.05$, and ** = $p < 0.01$ ([18] with permission).

3.3. Rat/3

3.3.1. CO₂ inhalation

During CO₂ inhalation increases in REG and LDF were significant, while carotid flow and systemic arterial pressure decreased. The transient increases in REG pulse amplitude ($69 \% \pm 2.6$) and LDF ($78.1 \% \pm 4.4$) were highly significant ($p < 0.001$), Fig. 6 and Table 1 and 2.

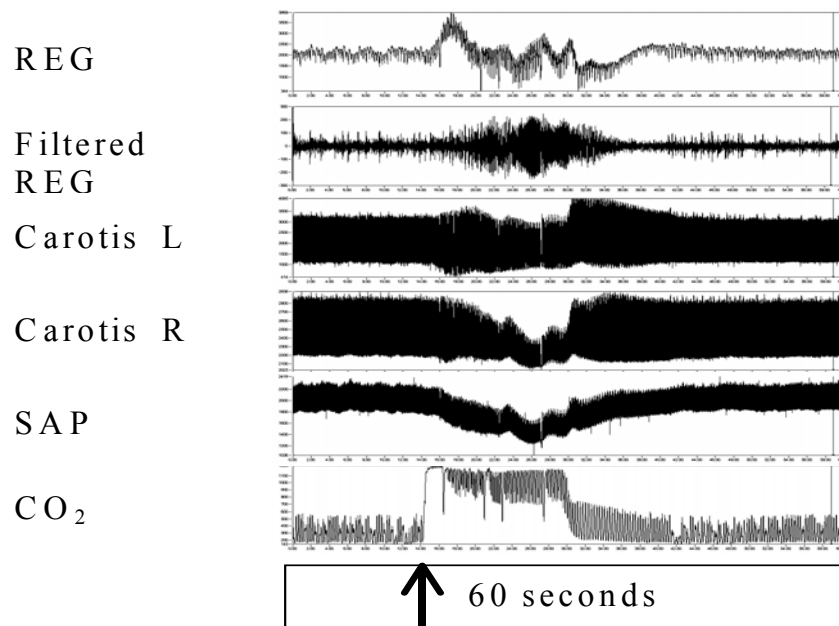


Figure 6. REG pulse amplitude increases during CO₂ inhalation (subgroup A). Filtered REG: rheoencephalograph after removal of the respiratory subharmonic, Carotid L and R: left and right carotid arterial flow, SAP: systemic arterial pressure, CO₂: exhaled carbon dioxide and at the arrow: 10 % inhaled CO₂ during 1 s. Time window: 60 s. The rat/file ID was: 157 – 3.

Table 1. REG integral increase during CO₂ inhalation (subgroup B).

Rat ID	BL	MAX	Increase %
158-1	0.071	0.196	176.06
158-2	0.097	0.278	186.60
158-3	0.109	0.341	212.84
158-4	0.1	0.324	224.00
157-1	0.079	0.586	641.77
157-2	0.133	0.454	241.35
157-3	0.141	0.508	260.28
157-4	0.112	0.383	241.96
7-2-1	0.061	0.221	262.30
7-2-2	0.012	0.031	158.33
7-2-3	0.639	2.491	289.83
8-1-1	0.04	0.066	65.00
8-6-1	0.101	1.562	1446.53
8-6-2	0.191	2.311	1109.95
8-6-3	0.01	0.072	620.00
8-6-4	0.01	0.063	530.00
8-6-5	0.011	0.059	436.36

Rat ID: identification of a rat/trial; BL: value of 5-second baseline REG integral; MAX: value of 5-sec integral during maximal REG amplitude; Increase: value expressed as percentage of BL. The group average increase was 417.83 ± 366.74 . Total number of rats was 5; total number of trials was 17. The increase was expressed as percentage of BL; it was significant ($p = 0.0048$). The Pearson correlation coefficient was 0.79, and the Spearman correlation coefficient was 0.88. The p-value associated with each correlation was less than 0.0001.

Rat ID	Number of time points	Pearson's (r)	Spearman's (r)
7/11/02	29	0.63	0.73
7/18/02	29	0.80	0.74
7/23/02	35	0.71	0.66
7/25/02	24	0.63	0.81
Total	117	2.77	2.94
Mean	29.25	0.69	0.74
SD	4.50	0.08	0.06

Table 2. **Statistical summary of the CO₂ inhalation results in REG/LDF group.** The 10 sec time window of the analyzed sample was characterized by 3 or 4 values. Pearson's (r) for all 117 time points = 0.80, Spearman's (r) for all 117 time points = 0.73. All correlations are statistically different from zero with a p-value less than 0.01. Rat ID: identification of a rat.

3.3.2. Carotid Clamping

Figures 7 and 8 show the effect of carotid artery clamping on REG amplitude and integral. During carotid artery clamping, the decrease in REG amplitude and integral were both highly significant ($P < 0.0001$).

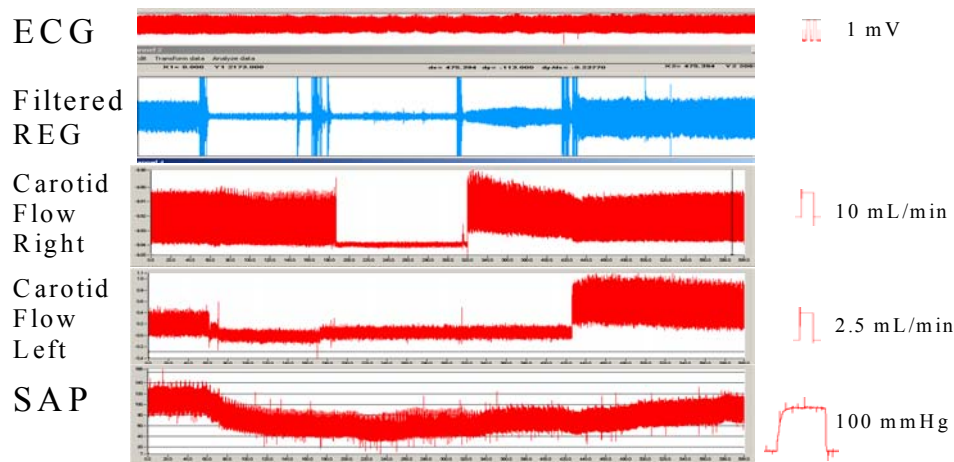


Figure 7. Effect of clamping of common carotid arteries. Following the first clip placement on the left carotid artery, the rheoencephalogram (REG) amplitude (Filtered REG) decreased; the placement of the second clip right carotid artery had no further decrease. During the clamping period there was no pulse amplitude observed in either carotid trace. For better visibility the recording traces were blown up; the real flow calibration values appear on the right side. Amplification of left and right carotid flow differed. A few

minutes after removal of one clip from the right carotid artery, REG amplitude moderately increased, and after removal of the second clip from the left carotid artery, the REG amplitude returned to slightly above the baseline level. Similarly, both carotids showed a slight hyperemic reaction. The baseline systemic arterial pressure (SAP) value was 135/80 mm Hg; during clamping, the minimal value was 80/40 mm Hg. REG was an intrahemispherical (left side) derivation. The time window was 10 min; REG Filter was 3-100 Hz. ECG: Electrocardiogram. The rat/file ID was 5-23-02/11.

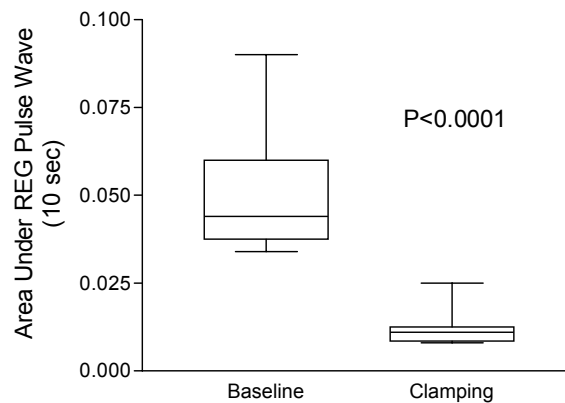


Figure 8. REG integral before and during carotid clamping. Data are expressed as a percentage of baseline. Mean decrease: 27.53 %, SEM: 0.05, SD: 0.1804.

3.3.3. Hemorrhage

During hemorrhage, REG transiently increased ($147\% \pm 44$; $p=0.037$), while cortical flow (measured by laser Doppler) ($78\% \pm 45$; $p=0.046$) and carotid flow (52 ± 7.5 ; $p=0.005$) decreased and correlated with systemic arterial pressure, Fig. 9.

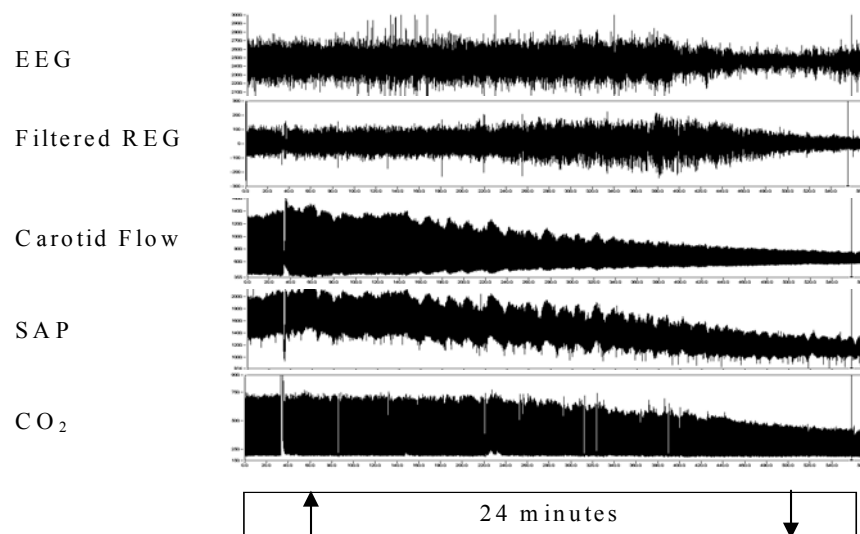


Figure 9. REG pulse amplitude increase during hemorrhage.

Arrows indicate start and end of SAP decrease to 40 mmHg. Carotid flow decreased similarly to SAP without showing any sign of CBF autoregulation. REG amplitude transiently increased then decreased, demonstrating CBF autoregulation and indicating its lower limit before 40 mmHg SAP. The EEG amplitude decrease coincides with the disruption in brain activity coincident with the diminished CBF status. EEG: electroencephalogram, Filtered REG: left side, after removal of respiratory subharmonic, Carotid Flow: left side, SAP: systemic arterial pressure, CO₂: exhaled carbon dioxide. Time window: 24 m. The rat/file ID was: 174-CO3.

3.4.Pig

During aortic occlusion (caused by abdominal compression) the systemic arterial blood pressure increased 59.67 ± 11.92 percent (mean \pm SD; $p = 0.008$), LDF increase was non-significant 10.75 ± 2.21 % (mean \pm SD; $p = 0.089$), and REG decreased 23.75 ± 8.18 % (mean \pm SD; $p = 0.01$), Fig. 10.

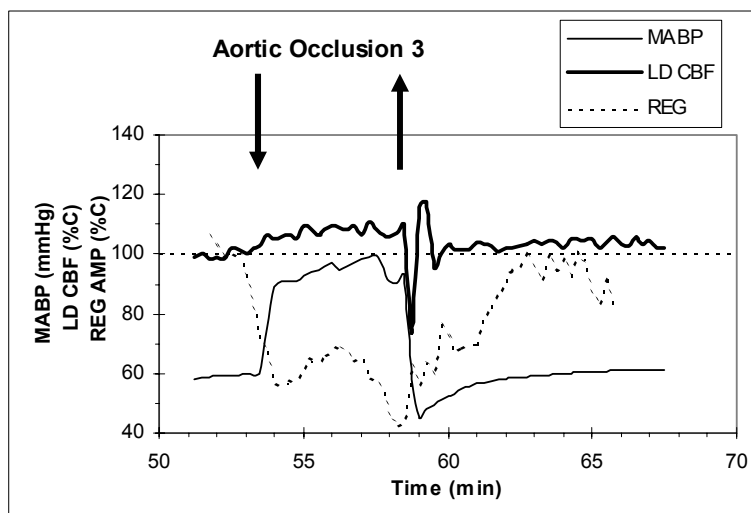


Figure 10. A typical effect of the compression of abdominal aorta in a pig. During the 5-min compression (start and end indicated by arrows), mean arterial blood pressure (MABP) increased; local CBF measured by LDF (LD CBF) increased; and global CBF measured by REG amplitude (REG), decreased. This global CBF decrease is the demonstration of CBF autoregulation. MABP Y-axis is mmHg, LD CBF; REG values are expressed as a percentage of the baseline (% C) ([18] with permission).

4.0. DISCUSSION

4.1. Challenges

CBF was altered with stimuli known to cause increases in CBF: CO₂ inhalation and brain electrical stimulation. Clamping of the common carotid arteries decreases CBF. The CBF autoregulation was additionally tested by hemorrhage causing blood pressure decrease, resulting brain vasodilatation, and aorta compression causing blood pressure increase resulting brain vasoconstriction. For details see 4.2.1.

4.2. CBF

The brain has ongoing, substantial energy requirements but minimal stores of energy-generating substrates. As a result, it is completely dependent on a continuous, uninterrupted supply of substrate (oxygen, glucose). Although the demand by the brain for energy-generating substrates is substantial (the central nervous system consumes 20% of the oxygen or 170 mmol/100 g per min or 3-5 ml O₂/100 g brain tissue per mm or, approximately, 40-70 ml O₂/min) and 25% of the glucose (31 mmol/100 g per mm) utilized by the resting individual under physiological conditions, this is met more than adequately by the 15% of the resting cardiac output (750 ml/min) which perfuses the brain (mean global CBF) = 50 ml/100 g brain tissue per mm (range 45-55 ml/100 g per mm) approximately 80% to grey matter and 20% to white matter). Indeed, normally, the supply of oxygen (approximately 150 ml O₂/min) is considerably in excess of requirements (around 40-70 ml O₂/min) such that the brain extracts only 25-30% of that supplied. In addition, the brain can conserve energy and, hence, decrease demand by switching off many of its metabolic processes before its reserves have been compromised when the delivery of substrate reaches 'critical' values. However, the flip side of this argument is that, paradoxically, the brain cannot tolerate significant increases in the volume of the contents of the rigid container in which it is enclosed. Moreover, because the brain's own store of energy-generating substances (glycogen, glucose, oxygen) is small (so small that, at normal rates of adenosine triphosphate production, the stores of glycogen in the brain would be exhausted in less than 3 min) it is uniquely dependent on a continuing, and adequate, supply of substrate [19].

4.2.1. CBF Autoregulation

Autoregulation in the cerebral circulation may be defined more pragmatically as the mechanism that protects the brain against the dangers of hypoxia at low perfusion pressures and against the risks of brain edema at high arterial pressures. Based on this definition, cerebral autoregulation may be thought of as a homeostatic mechanism that is superimposed over and above the baroreceptor reflexes. The baroreceptors, strategically located at the most proximal locations in the cerebral circulation, provide the first line of defense against acute ranges in arterial pressure. Autoregulation then serves as the next line of defense by helping to maintain constant cerebral capillary pressure, thus assuring a steady supply of essential metabolites and simultaneously protecting the blood-brain barrier. Several hypotheses (myogenic, neurogenic, and metabolic) have been proposed to account for the mechanisms that underlie autoregulation, detailed elsewhere [20].

The anatomical foundation of CBF autoregulation is the arteriole. The arterioles are the last small branches of the arterial system, and they act as control valves through which blood is released into the capillaries. The arteriole has a strong muscular wall that is capable of closing the arteriole completely or of allowing it to be dilated several fold, thus having the capability of vastly altering blood flow to the capillaries in response to the needs of tissue [21,22]. This arteriolar functioning is visualized by functional MRI in brain imaging [23].

REG showed the classical CBF autoregulatory response, indicating its close relationship to arteriolar changes. Early CBF-REG studies did not focus on this topic [24-27].

4.2.2. CBF and CO₂

In man, 5% and 7 % CO₂ inhalation raises CBF by approximately 50 and 100 %, respectively [10]. Cerebral vasodilatory responses to hypercapnia and hypoxia are consistent, reproducible and reversible. Accordingly, changes in systemic gas tensions have been frequently employed as a test of essential cerebrovascular reactivity under normal and pathophysiologic conditions. The mathematical expressions that govern the relationship between CBF and partial pressure of carbon dioxide have been described [11, 28]. In these

experiments we demonstrated that REG detects CBF (and/or volume) increase during CO₂ inhalation, similarly to other quantitative CBF techniques.

4.2.3. CBF and Hemorrhage

The vital functions of the brain, in spite of its well-developed autoregulation, are impaired during prolonged hypovolemic conditions as the CBF autoregulatory reserve is exhausted. Afferent neural input to the brain seems to be elevated during shock. It may be presumed that this leads to increased tissue metabolism and the accumulation of metabolites. The low flow combined with elevated neuronal activity and cellular metabolism produces an imbalance between oxygen delivery and oxygen utilization [29] leading to neuronal damage.

Cerebrovascular responses to hemorrhage reflect the balance between autoregulatory vasodilatation and sympathetic vasoconstriction [30]. During hemorrhage CBF heterogeneity [31] and hypovolemic cerebral hyperemia was observed [32]. In hemorrhagic hypotension the shift of CBF autoregulation is described [20]. In our experiments during hemorrhage only REG showed the classical CBF autoregulation: LDF and carotid flow followed SAP decrease during hemorrhage. It would appear from these responses that the REG responses may best be explained if the REG signal is a vascular volume measurement as opposed to a measure of blood flow. This would explain why the REG and LDF measures may change in apparently opposite directions, such as that encountered in the case of hemorrhagic hypotension.

4.3. REG

The physical basis of the electrical impedance method is based on the fact that blood or cerebrospinal fluid are better conductors than the brain or other 'dry' tissue. The electrical impedance method (measuring blood flow by alternating current) is known in clinical practice, however it is used mostly in cardiology and for measuring peripheral circulation. When used on the head, it is called rheoencephalography, REG [26]. REG is based on monitoring pulse synchronous variations in cranial electrical impedance over time. Various correlations were established between REG and CBF (volume, flow or pressure, detailed by [26]. REG pulse amplitude is quantified most frequently using its derivative [9,24,25] or integral. Both variables detect the applied CBF manipulations. The application of the REG derivative and integral has an advantage using computer data processing. Other potential REG processing methods [33] have resulted in no practical improvement. According to an earlier WRAIR publication, REG can be used for ICP monitoring [6]. Additionally, recent results suggest that noninvasive cerebral impedance measurements do reflect intracranial events, and are able to detect cerebral edema following hypoxia-ischemia [34].

One technical problem with the REG instrumentation used in this study is with regard to the fact that the REG device (except in Rat/1 group) with bipolar derivation is able to measure AC, i.e. pulsatile impedance only. The basic impedance is compensated at the beginning of the measurement in such type of impedance amplifiers, so they are unable to record the DC component as a signal. This prevents detection of changes in the DC portion of the signal, which are related to the overall brain volume. The tetrapolar devices are able to record basic impedance and consequently detect the absolute volume changes, as they are used in clinical practice for venous outflow phlebography or impedance cardiography.

In order to avoid potential interference with extracranial circulation here we used intracerebral REG derivations, only. We plan to study the relationship of intracerebral and surface derivations.

4.4. Monitoring

The primary aim of managing patients with acute brain injury in the intensive care unit is to minimize secondary injury by maintaining cerebral perfusion and oxygenation. The mechanisms of secondary injury are

frequently triggered by secondary insults, which may be subtle and remain undetected by the usual systemic physiological monitoring. Continuous monitoring of the central nervous system in the intensive care unit can serve two functions. Firstly it will help early detection of these secondary cerebral insults so that appropriate interventions can be instituted. Secondly, it can help to monitor therapeutic interventions and provide online feedback [35]. On the battlefield the Doppler CBF test (or other clinically used CBF measurement, such as fMRI, SPECT, PET scan) is not realistic due to size and weight considerations.

From our previous experiment [36] it is known that the information content of REG can be different, depending on the physiological or pathophysiologic range of CBF autoregulation. The REG signal reflects the electrical conductivity within the cranial cavity. Pathophysiologic changes influence the normal conductivity [27]. Our recent data obtained during CO₂ inhalation were collected in the physiological range, consequently, one cannot draw any conclusions regarding what will be shown under pathophysiologic conditions such as hemorrhage or elevated ICP. Similarly, there is no comparative data examining the difference between local and global CBF and carotid flow during the above conditions. For noninvasive blood flow monitoring purposes, there is a need to clarify the potentially useful CBF monitoring modality (possibly global flow - REG) and examine the relationship between CBF, SAP, ICP, and EEG. Non-invasive monitoring, including cardiac impedance measurement, revealed low-flow and poor tissue perfusion that was worse in the non-survivors (on high-risk elective surgery patients, [37].

4.5. Technical Remarks

In clinical practice the CBF autoregulation is measured as a routine test using Doppler ultrasound [38]. Doppler technique, as it is used in today's clinical practice, is not applicable in military environments. The REG CNS monitoring method is more suited for military environments because of its non-invasiveness, good time resolution and potential for miniaturization. Although several CBF-REG correlative studies have shown that it is possible to quantify CBF measured by REG [24-27], the studies reported here suggest that its utility would appear to be more related to its relationship to cerebrovascular reactivity (CBF autoregulation). Therefore, interpretation of the REG signal alone, without knowledge of the perfusion pressure or SAP, is difficult. However, under normotensive conditions, or steady state blood pressure conditions, changes in REG amplitude would be expected to correlate with changes in cerebral blood flow.

The key question then is whether REG measures volume or flow. The definition invoked by the FDA [39] states: Sec. 882.1825. "Rheoencephalograph: (a) Identification. A rheoencephalograph is a device used to estimate a patient's cerebral circulation (blood flow in the brain) by electrical impedance methods with direct electrical connections to the scalp or neck area." In other words it specifically defines REG as a measure of flow and this is the reason why we used flow in the text. On the basis of previous and recent data [40-42], however, a more practical definition would use volume rather than flow. This statement is supported by human and animal measurements as well [36].

In the potentially applicable REG electronics and software used in the Cerberus system [8], the EKG signal is synthesized from impedance electrodes located on the upper arms and legs. In this case, the electrodes (conductive elastic fabrics sewn into a uniform) are multifunctional sensors; a 2-channel bio-impedance signal can be used to generate a pulse wave, an EKG, a respiratory trace and a pulse wave transmission time, which could potentially provide noninvasive blood pressure information [43].

5. 0. CONCLUSIONS

Animal studies confirmed that REG qualitatively reflects changes in CBF during physiological perturbations known to alter CBF. The results are consistent with REG being a reflection of cerebrovascular responsiveness as opposed to the local CBF changes shown with LDF or carotid flow. Because of the CBF heterogeneity, only global CBF would be suitable for monitoring purposes.

REG monitoring may be a useful, non-invasive, continuous monitoring method of assessing global CBF and cerebrovascular reactivity or capacitance for combat casualty care of victims suffering from hemorrhage and may have applicability for maintaining cerebral blood flow in non-combat medicine as well. Further work will focus on correlating brain function: EEG and CBF/REG assessments [44-48] during hemorrhage and resuscitation, using various resuscitation fluids. Further studies are needed to test the CBF autoregulation with graded increases in intracranial pressure, a common consequence of traumatic brain injury [49-54].

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